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6-Bicyclopiperazinyl-1-arylsulfonylindoles and 6-Bicyclopiperidinyl-1-arylsulfonylindoles Derivatives as Novel, Potent, and Selective 5-HT_6 Receptor Antagonists

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Abstract—A novel series of 6-bicyclopiperazinyl-1-arylsulfonylindoles and 6-bicyclopiperidinyl-1-arylsulfonylindoles derivatives was synthesized and found to be potent and selective 5-HT_6 receptor antagonists.

The human 5-hydroxytryptamine$_6$ (5-HT_6) receptor, one of the most recently cloned serotonergic receptors, is a 440-amino acid polypeptide with seven transmembrane spanning domains typical of the G-protein-coupled receptors. It is one of the 14 receptors that mediate the effects of the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin).[1] Within the transmembrane region, the human 5-HT_6 receptor shows about 30–40% homology to other human 5-HT receptors and is found to be positively coupled to adenylyl cyclase.

The prominent localization of 5-HT_6 receptor mRNA in the nucleus accumbens, striatum, olfactory tubercle, substantia nigra, and hippocampus of the brain,[2] together with its high affinity for several therapeutically important antipsychotics and antidepressants suggest a possible role for this receptor in the treatment of schizophrenia and depression. In fact, the prototypic atypical antipsychotic agent clozapine exhibits greater affinity for the 5-HT_6 receptor than for any other receptor subtype.[3]

Although the 5-HT_6 receptor has a distinct pharmacological profile, in vivo investigation of receptor function has been hindered by the lack of selective agonists and antagonists. Recent experiments demonstrated that chronic intracerebroventricular treatment with an antisense oligonucleotide, directed at 5-HT_6 receptor mRNA, elicited a behavioral syndrome in rats consisting of yawning, stretching, and chewing. This syndrome in the antisense-treated rats was dose-dependently antagonized by atropine (a muscarinic antagonist), implicating the 5-HT_6 receptor in the control of cholinergic neurotransmission. Therefore 5-HT_6 receptor antagonists may be useful for the treatment of memory dysfunction.[4]

Recently, Ro 04-6790 **1**, Ro 63-0563 **2**,[5] and SB-271046 **3**[6] were reported as selective 5-HT_6 receptor antagonists. However, compounds **1** and **2** have only moderate potency at the rat 5-HT_6 receptor and were found to be poorly brain penetrant. Compound **3**, on the other hand, has relatively high affinity for the 5-HT_6 receptor, but pharmacokinetic studies indicate that it was only moderately brain penetrant.

As part of our research program directed toward the design and synthesis of potent and selective 5-HT_6 receptor antagonists, we discovered a novel series of 6-bicyclopiperazinyl-1-arylsulfonylindoles and 6-bicyclopiperidinyl-1-arylsulfonylindoles derivatives. We herein report the synthesis and biological activity of these novel 5-HT_6 receptor antagonists.

Chemistry

The 6-bicyclopiperazinyl-1-arylsulfonylindoles **4a**–**h** were synthesized as shown in Scheme 1. *N*-Silylation of 6-bromoindole **5** with triisopropylsilyl chloride (TIPS-Cl) yielded **6**, which was subjected to the conditions of metal-catalyzed aryl amination[7] to give **7**. Subsequent desilylation of **7** afforded **8**, which was then sulfonylated to give **4**.

The corresponding piperidine analogues were synthesized according to Scheme 2. The indole **5** was coupled to the

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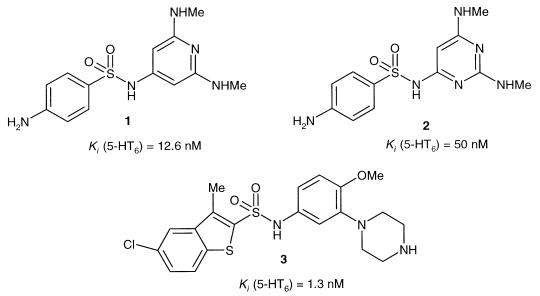
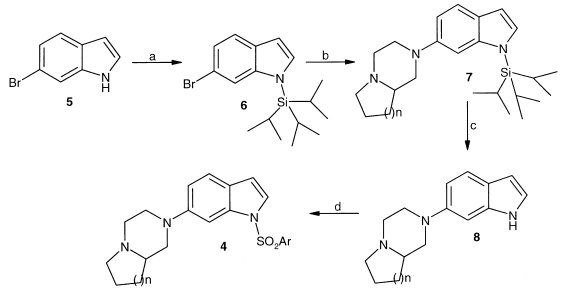
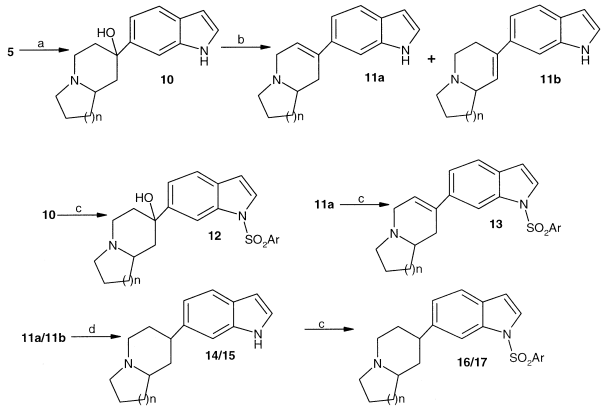


Figure 1.



Scheme 1. (a) NaH, TIPS-Cl, DMF, 0 °C; (b) bicyclopiperazine, NaO*t*-Bu, $Pd(OAc)_2$, *t*-Bu_3P, Xylene, 120 °C; (c) TBAF, THF; (d) NaHMDS, $ArSO_2Cl$, THF.



Scheme 2. (a) KH, *t*-BuLi, **9**, THF, −78 °C; (b) TFA, THF; (c) NaHMDS, $ArSO_2Cl$, THF; (d) H_2, Pd/C, MeOH.

bicyclopiperidone **9** to give the carbinol **10**. Compound **10** was then treated with trifluoroacetic acid to effect the elimination to alkenes **11a** and **11b**. Both intermediate **10** and **11a** were subjected to aryl sulfonylation to give **12** and **13**, respectively. Palladium catalyzed hydrogenation of **11a** and/or **11b** gave two diastereoisomers **14** and **15**, which were easily separated by column chromatography. Arylsulfonylation of the diastereoisomers gave **16** and **17** (designated as the more polar and less polar isomers, respectively).

Biological activity

All compounds were evaluated in vitro for their 5-HT_6 receptor binding affinity (Table 1). The assay protocol entails the incubation of membranes, prepared from HEK293 cells expressing the human 5-HT_6 subtype of receptor, with ^{3}H-LSD and using clozapine, a typical 5-HT_6 receptor antagonist, as a standard. Specific concentrations of the test compounds were incubated with the radioligand (^{3}H-LSD) and the receptor affinity (K_i in nM) was determined.

Table 1. Structure and binding of the 6-bicyclopiperazinyl-1-arylsulfonylindoles and the 6-bicyclopiperidinyl-1-arylsulfonylindoles

Compound	*n*	Ar	K_i (5-HT_6, nM)[a]
4a	1	1-Naphthyl	0.2
4b	1	*p*-Tolyl	3.3
4c	2	1-Naphthyl	1.7
4d	2	2-Naphthyl	3.0
4e	2	2,4-diF-phenyl	3.6
4f	2	Phenyl	5.7
4g	2	*p*-Tolyl	4.9
16	1	1-Naphthyl	0.8
17	1	1-Naphthyl	0.6
13	1	1-Naphthyl	1.3

[a]K_i values are given as the mean of at least two independent determinations performed in triplicate with less than 15% deviation.

Table 2. Receptor binding profile of compound **4a** (Affinity in% inhibition at 100 nM)

5-HT_{1A}	79	5-HT_7	8
5-HT_{1B}	2	$M_1 + M_2$	0
5-HT_{1D}	5	D1	1
5-HT_{1F}	9	D2	7
5-HT_{2A}	32	D3	22
5-HT_{2B}	36	D4	0
5-HT_{2C}	17	D5	0
α1	0		

In general, all of the compounds tested above were found to be very potent at the 5-HT_6 receptor with K_i's less than 10 nM. In the case of the bicyclopiperazines (**4a**–**g**), the 5,6-bicyclopiperazines were more potent than their corresponding 6,6-bicyclopiperazine. For example, **4a** ($K_i = 0.2$ nM) and **4b** ($K_i = 3.3$ nM) have a greater affinity for the 5-HT_6 receptor than their bicyclic homologue **4c** and **4g**, with K_i's of 1.7 nM and 4.9 nM, respectively. The binding results on the representative selection of the 6,6-bicyclo-derived sulfonylated indoles **4c**–**4g** are shown in Table 1. Of the monocyclic and bicyclic aromatic sulfonyl groups studied, the lipophilic bicyclic substituent such as the 1-naphthyl group were beneficial to 5-HT_6 receptor activity. The rapid optimization of the aryl sulfonyl groups (1-naphthyl group favored) along with the realization that the 6,5-bicyclopiperazine-systems were generally more potent than the corresponding 6,6-bicyclopiperazine homologue, prompted us to examine the 6,5-bicyclopiperidine analogues (**16** and **17**). Both isomers **16** and **17** demonstrated subnanomolar 5-HT_6 receptor affinity (K_i of 0.8 nM and 0.7 nM, respectively). In addition, the 6,5-bicyclopiperidine analogues **12** and **13** maintained good 5-HT_6 receptor activity (K_i of 4.7 nM and 1.3 nM, respectively) further indicating the degree of structural variations allowed without compromising 5-HT_6 receptor affinity.

In the functional adenylyl cyclase assay, the most potent compound **4a** was found to be a competitive antagonist

($IC_{50} = 7.2$ nM) with good binding selectivity over a number of other key receptors (Table 2).

In conclusion, a novel series of potent and selective 5-HT_6 receptor antagonist has been developed. The compound **4a** was the most potent compound from the series and has demonstrated good in vitro receptor selectivity thus making it a promising candidate for the possible treatment of schizophrenia, depression and memory dysfunction. Compound **4a** is currently being further evaluated for its therapeutic potential.

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